HealthTech IV

Cooperative Agreement #GPH-A-00-01-00005-00

Semiannual Report
April 2005 – September 2005

Submitted to:
United States Agency for International Development (USAID)

Submitted by:
Program for Appropriate Technology in Health (PATH)
1455 NW Leary Way
Seattle, WA 98107

November 14, 2005

PATH
A catalyst for global health

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Highlights and Milestones of the Past Six Months

- HealthTech has launched an active technical development phase in collaboration with the Instituto Biologico Argentino SAIC (BIOL) to conduct preliminary studies of oxytocin in the Uniject™[1] device and plan for the more extensive formal stability studies expected to begin in December 2005. Unless there are very unexpected results from these studies, BIOL should be able to provide initial supplies of oxytocin in the Uniject device for field study use by mid-2006.
- PATH, under HealthTech, contributed significantly to a World Health Organization (WHO)-issued draft policy document entitled "Safe vaccine chain for the prevention of freezing and the improvement of immunization coverage." PATH-initiated components include the extensive data on the need for cold chain temperature monitoring studies, use of chilled water packs for vaccine transport, options for vaccine transport at ambient temperatures, and guidelines for operating and loading refrigerators to prevent freezing. WHO also posted on its website a protocol for assessing temperatures in the vaccine cold chain, based on the HealthTech protocol for this.
- With HealthTech assistance, Indonesia held a national-level workshop on vaccine freezing and finalized its approach to freeze prevention.
- With cofunding from UNICEF and HealthTech, PATH completed a study of temperature monitoring in Bolivia's cold chain. Results showed freezing temperatures in all shipments regardless of climate or elevation.
- HealthTech staff completed the Senegal evaluation of acceptability of needle removers and sharps barrels, and results have been posted on TechNet. The study found that health workers preferred needle removal over putting the complete needle and syringe into the safety box. One advantage was reduction in the number of safety boxes needed, since 50 percent more defanged syringes fit into a safety box than syringes with needles. The study also validated the use of the sharps barrel in areas where needle pits are not appropriate or acceptable. The barrel provides a good option in areas where high water table, rocky ground, or the lack of open ground prevents the digging of pits.
- HealthTech also completed an evaluation of acceptability, fit, and function of a disposable needle-removal device, the Hub Cutter, to be used as part of a safe injection package in clinic settings in Uganda where family planning and other services are delivered. The device was well accepted by study participants who reported that it was extremely dependable and easy to use. Health workers and waste handlers described an increase in the overall cleanliness of their health facilities with the introduction of the Hub Cutter. The Hub Cutter effectively reduced volumes of clinical waste by approximately 35 percent and allowed consideration of infectious waste bags for disabled syringe barrels. The Hub Cutter's unique features may be of greater benefit as part of outreach efforts or in remote, rural settings.

[1] Uniject is a trademark of BD.

- The study of the retinol binding protein immunoassay (RBP-EIA), the test for vitamin A deficiency (VAD), in Thailand has been completed. Results showed the first evidence of the biological comparability between serum retinol levels estimated from venous blood and capillary blood. This knowledge adds to a growing body of research that has demonstrated close correspondence between retinol in venous blood samples and RBP in capillary blood.
- HealthTech also completed data analysis of dried blood spots stability study conducted in Tanzania. Correlation and validity of the RBP-EIA test performed in a laboratory in Tanzania were similar to tests performed in the United States. Serum RBP correlated well with high-performance liquid chromatography (HPLC) serum retinol concentrations. Sensitivity was high at 92.5 percent, while specificity was only moderate (65.2 percent). The association between serum retinol and RBP did not change after adjustment for infectious disease or signs of malnutrition.
- A summary of evidence document has been written. The summary compiles evidence of the performance of the RBP-EIA compared to retinol using different sample types that have been conducted over the past five years. The data support the use of RBP-EIA as an alternative measure for VAD, compared to retinol analyzed using HPLC.
- A screening and compatibility study of gentamicin in the Uniject device has been initiated with a qualified and interested bulk supplier of gentamicin—Instituto Biologico Argentino SAIC (BIOL) in Argentina. Preliminary interim data at the six-week mark appears promising for two of three buffering systems under evaluation. If a stable formulation is identified, HealthTech and BIOL would complete documentation to facilitate supply for field evaluation and eventual registration of the product for commercial supply.
- Laboratory and user evaluations of a selection of neonatal resuscitators were carried out. User evaluations demonstrated the usability of different device designs and highlighted differences between tube and mask and bag and mask resuscitators. *Practical selection of neonatal resuscitators, A field guide*, comparing 11 resuscitators, was completed and will be useful to program managers and health workers making procurement decisions.
- A study of the rapid chlamydia test, developed under HealthTech, was launched in collaboration with the Population Council in Bolivia. This evaluation will determine the sensitivity and specificity of the test in uncontrolled clinical settings. It will also determine the utility of new sample collection devices with our test. Approximately 1,800 women will be screened with the test.
- The technology transfer recipient of the rapid gonorrhea test—Orchid Biomedical of India—has collaborated with HealthTech on enhancements to the test, which have improved sensitivity by 30 times over the original test.
- A study of cleaning and disinfection of cautery tips to determine feasibility for reuse indicates that cautery tips can be effectively cleaned and disinfected with bleach through standard reprocessing procedures. The data were used then to prepare instructional materials and a job aid on reuse of cautery tips which have now been distributed through a poster on the PATH website.

- HealthTech continued monitoring of Pfizer's progress towards adopting the Uniject device as the delivery mechanism for their subcutaneous formulation of DMPA to be supplied to USAID. The use of this device for delivery of DMPA would greatly improve accessibility and ease of delivery, possibly allowing home injection. Pfizer has completed their technical and manufacturing feasibility investigation of full-scale production of DMPA in the Uniject device with positive results. BD is prepared to begin supplying the Uniject device to Pfizer as soon as Pfizer decides to move forward.

Milestones and Accomplishments for Past HealthTech Technologies

- One major effort under HealthTech the past six months was the completion of the formal review of USAID's investment in technologies which mainly focused on the 18-years of the HealthTech program at PATH. To prepare for the meetings, staff wrote and produced an extensive briefing document, which provides substantive evidence of impact and results of the program over time.
- In summary, HealthTech has developed or is currently developing 38 technologies and has adapted from existing technologies or codeveloped with other entities 21 others. Over 26 technologies have been commercialized and advanced. Currently 19 are known to be sold and in distribution globally or regionally, for a total of 3.8 billion units sold. More details are available in the briefing document entitled "Review of the HealthTech Program after 18 Years."
- The *Bulletin of the World Health Organization* published "The costs of home delivery of a birth dose of hepatitis B vaccine in a prefilled syringe in Indonesia" (June 2005) authored by Carol Levin of PATH. The cost study was supported by non-HealthTech funds but focused on delivery of vaccine with HealthTech technology—the Uniject device.
- An abstract on the Birthweigh III was accepted for the World Congress of Epi in Thailand in August. Entitled "A low-cost, color-coded, hand-held spring scale accurately categorizes birth weight in low-resource settings," it was coauthored by HealthTech staff and colleagues from Johns Hopkins and the Saving Newborn Lives program of Save the Children. The results of the study showed that the device provides an important method to identify low birth weight infants in low-resource settings where deliveries occur primarily in the home. Availability of this scale makes feasible, for the first time, programmatic targeting of community-based interventions for high risk newborns, for example, topical emollient therapy, chlorhexidine skin cleansing, and kangaroo mother care. Additionally, this device will enable the provision of interventions requiring dose-adjustment according to weight, such as antibiotic therapy or micronutrient supplements.

Strategic Objective 1

Introduction of Injectable Contraceptives in the Uniject Device

Health Need Addressed

Injectable contraceptives are becoming increasingly popular around the globe as women search for safe, highly effective, reversible methods of contraception that do not require compliance with a daily regimen. Depot medroxyprogesterone acetate (DMPA) is administered by injection once every three months, making it highly convenient. Cyclofem®[1] injectable contraceptive (also known as Lunelle and CycloProvera) is administered by injection every month and is formulated to allow women to have more normal menstrual cycles—an advantage in many cultures. Currently, international development and family planning agencies purchase over 25 million doses of DMPA injectable contraceptives annually for distribution to family planning programs throughout developing countries. Approximately 7 million doses of Cyclofem injectable contraceptives were sold in the year 2000.

International development and family planning agencies and recipient governments are continually looking for feasible and affordable methods to reduce unsafe injection practices that can lead to the spread of bloodborne diseases. Provision of one sterile needle and syringe with every dose of injectable contraceptive is the current standard. However, there is a risk with disposable syringes that they will be reused. Autodisable (AD) syringes prevent reuse, but like disposable syringes they can be diverted to other uses during the distribution process. The Uniject™[2] prefill injection device has distinct advantages in terms of both safety and procurement.

HealthTech IV Solution and Potential Impact

A decade ago, prefilled syringes were too costly for use in public-sector health programs, and no prefilled syringe on the market offered an AD feature. Under the HealthTech project, PATH was able to develop the Uniject device, a proprietary, prefilled, AD injection system. The Uniject device prevents reuse, simplifies matching of syringes and supplies, ensures dose accuracy, and is so simple to use that injection at home by the patient or a family member is feasible. Now the device is being considered for use filled with injectable contraceptives. With funding from the USAID Office of Population, PATH has been working for a number of years with the dominant international supplier of DMPA injectable contraceptive to evaluate potential use of the Uniject devices. This company was Pharmacia until it merged with Pfizer in April 2003. PATH has also worked with Aplicaciones Farmacéuticas, a Mexican pharmaceutical company which has developed but not yet launched a version of its once-a-month injectable contraceptive, Cyclofem, in the Uniject device.

[1] Cyclofem is a registered trademark of The Concept Foundation.
[2] Uniject is a trademark of BD.

Ultimate Goals and Objectives of HealthTech Project

- To increase the safety, acceptance, and reach of DMPA injectable contraceptives in family planning programs.
- To enable innovative new family planning program options, such as home injection and outreach.

Status of Project as of September 2005

- Pfizer has completed technical and manufacturing feasibility investigation of full-scale production of their subcutaneous formulation of DMPA in the Uniject device (hereafter called DMPA-Uniject) with positive results.
- BD is prepared to begin supplying the Uniject device to Pfizer at any time.
- The immediate critical issue facing this project (and product) is the inability of Pfizer and BD to negotiate mutually acceptable terms for a long-term supply agreement for the Uniject device. BD is extremely sensitive about any risk of violating US and European antitrust regulations as BD recently paid a $100+ million judgment relating to antitrust issues. Pfizer is extremely concerned about securing exclusive supply rights from BD for the Uniject device for a significant portion of the injectable contraceptive market in order to protect their large projected investment. The companies are delicately and slowly trying to work through these highly charged, often contradictory positions.

Milestones expected in the past six months	Achievements and progress towards milestones
BD and Pfizer conclude commercial negotiations.	No agreement yet. Progress dependent on BD-Pfizer pace. PATH has had ongoing interaction with both to encourage resolution as soon as possible.
PATH provide formal concurrence with exclusivity terms of BD-Pfizer agreement.	Deferred until BD-Pfizer complete negotiations.
Identify and map key milestones and decision points in Pfizer's new-DMPA program (their work to develop, register, and scale up production for new-DMPA-Uniject). Emphasis is on the likely timing of availability of supplies of new-DMPA-Uniject to USAID.	Deferred until BD-Pfizer complete negotiations.
Provide USAID with updated background paper on volumes and trends in supply of injectable contraceptives to international donor agencies for distribution in developing countries.	Draft 75 percent complete.

Hold a collaborators meeting between USAID, PATH, Pfizer, and BD to review the timeline/decision-point diagram noted above and discuss collaborative activities in next phase of Pfizer work.	Deferred until completion of Pfizer-BD commercial negotiations.

Problems encountered	Actions taken or plans to resolve
BD-Pfizer negotiations for long-term supply and exclusivity agreement of Uniject for injectable contraceptives not completed during this six month period. Slow communication between these two large organizations.	Continue interaction with both; encourage resolution as soon as possible.

Milestones expected in the next six months	Planned activities to reach those milestones
BD and Pfizer conclude commercial negotiations.	Continue interaction with both parties to encourage resolution as soon as possible.
PATH provide formal concurrence with exclusivity terms of BD-Pfizer agreement.	Keep PATH president informed of status of negotiations; work with PATH Legal Affairs to provide formal organizational concurrence when appropriate.
Identify and map key milestones and decision points in Pfizer's new-DMPA program (their work to develop, register, and scale up production for new-DMPA-Uniject). Emphasis is on the likely timing of availability of supplies of new-DMPA-Uniject to USAID.	On hold pending conclusion of BD-Pfizer negotiations. Contact with Pfizer will be particularly important to this activity once underway; they will drive the process.
Provide USAID with updated background paper on volumes and trends in supply of injectable contraceptives to international donor agencies for distribution in developing countries.	Finalize and distribute this brief report to USAID by December.
Hold a collaborators meeting between USAID, PATH, Pfizer, and BD to review the timeline/decision-point diagram noted above and discuss collaborative activities in next phase of Pfizer work.	Timing contingent on conclusion of Pfizer-BD commercial negotiations.

Vasectomy Technologies

Health Need Addressed

Recently published evidence suggests that the rate of vasectomy failure (measured by unintended pregnancy) is around 4 percent[1,2] with methods commonly used globally. Incorporation of improved methods, such as fascial interposition and thermal cautery, could help lower the rate of failure and increase acceptance of vasectomy.

HealthTech IV Solution and Potential Impact

Family Health International (FHI) and EngenderHealth (EH) have recently published evidence confirming the clinical advantages of fascial interposition[3] and indicating possible additional advantages of thermal cautery.[4,5] To complement this research, PATH was asked to evaluate the physical durability and the potential for reuse of a thermal cautery device along with potential redesign or cost-reduction opportunities. The long-term goal of this collaboration is to permit introduction of a cautery vasectomy technique, in conjunction with recommended procedural and reuse methods, for introduction into low-resource settings.

Ultimate Goals and Objectives of HealthTech Project

- Verify that a cautery device (designated by the manufacturer as single use) is safe and effective for multiple uses.
- Provide technical assistance to other project partners for review of new devices, sourcing of generic devices, and with sperm analysis.
- Conduct an evaluation of the cost-effectiveness of different currently used vasectomy methods.

Status of Project as of September 2005

PATH is finalizing the findings from an evaluation of the cost-effectiveness of different vasectomy methods in low-resource clinics.

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[1] Wang D. Contraceptive failure in China. *Contraception*. 2002;66:173–178.
[2] Nazerali H, Thapa S, Hays M. Vasectomy effectiveness in Nepal: A retrospective study. *Contraception.* 2003;67:397–401.
[3] Sokal D, Irsula B, Hays M. Vasectomy by ligation and excision, with or without fascial interposition: A randomized controlled trial. *BMC Medicine.* 2004;2:6.
[4] Barone M, Chen-Mok M, Sokal D. Effectiveness of vasectomy using cautery. *BMC Urology.* 2004;4(1):10.
[5] Sokal D, Irsula B, Chen-Mok M, Labrecque M, Barone MA. A comparison of vas occlusion techniques: Cautery more effective than ligation and excision with fascial interposition. *BMC Urology* 2004, 4:12.

Milestones expected in the past six months	Achievements and progress towards milestones
Finalization of instructional materials on cautery tip reuse and distribution through posting on PATH and EH websites.	Job aid for reuse of cautery tip completed and distributed on PATH website and through network of interested service providers in low-resource clinics. Available at: http://www.path.org/files/TS_disinfection_jobaid.pdf.
Complete clinical visits and data analysis, and draft report on cost-effectiveness and practicality of the cautery vasectomy technique.	Data collection in all sites completed in June 2005. Report to USAID drafted in July-August and reviewed at PATH and FHI. The findings indicate that alternative methods to simple ligation and excision, such as fascial interposition and thermal cautery, provide an improvement in cost-effectiveness.

Problems encountered	Actions taken or plans to resolve
Data on cost-effectiveness received from Kenyan site was of poor quality.	Straightforward reporting on quality of data from Kenya and reduction of emphasis on quantitative data from this site.
Delay in obtaining technical review of cost-effectiveness study by an economist.	Multiple health economists at PATH solicited for review.

Milestones expected in the next six months	Planned activities to reach those milestones
Completion and distribution of final cost-effectiveness evaluation report.	Review and revisions by health economist (November 2005). Inclusion of supplementary, recently received information on the costs of cautery devices (November 2005).
Revision of cost-effectiveness report and submission to peer-reviewed journal.	Editing of cost-effectiveness report for style, clarity, and reduced content for journal submission (January 2006).

Sharps Waste Management for Family Planning

(See Sharps Disposal Technologies report under Strategic Objective 3)

Strategic Objective 2

Oxytocin in the Uniject Device

Health Need Addressed

Hemorrhage is the leading cause of maternal mortality and is a particular problem in home deliveries because the short response time makes referral impractical in most cases. The percentage of maternal deaths due to postpartum hemorrhage (PPH) has been reported as 25 percent in sub-Saharan Africa, 27 percent in West Africa, and 45 percent in Indonesia. Annually, approximately 130,000 women are known to die due to hemorrhage during childbirth.[1] The use of oxytocin for routine management of the third stage of labor can significantly reduce the incidence of PPH. Active management of the third stage of labor (AMTSL), which includes routine use of a 10-IU dose of oxytocin given intramuscularly, is recommended by the World Health Organization (WHO) for all institutional deliveries and home deliveries attended by a person with midwifery skills.[2]

HealthTech IV Solution and Potential Impact

A prefilled, nonreusable syringe, such as Uniject™[3] is thought to be a particularly appropriate system for delivering the life-saving benefits of oxytocin to women in peripheral health care settings and homes. This prefilled, easy-to-use, injection-ready format ensures that an accurate premeasured dose is given in a nonreusable, sterile device with minimal preparation and minimum waste. Based on evaluations in Lombok, Indonesia, midwives found oxytocin in the Uniject device (hereafter called "oxytocin-Uniject") to be safer and more convenient to use during home deliveries than traditional needle and syringe. This study, and results from an upcoming study in Vietnam, may indicate that oxytocin-Uniject can play a major role in facilitating adoption of AMTSL strategies, thus preventing maternal mortality due to hemorrhage.

Ultimate Goals and Objectives of HealthTech Project

Improve and ease adoption of AMTSL initiatives and therefore reduce PPH by engaging one or more pharmaceutical producers to supply oxytocin-Uniject commercially on an ongoing basis. Note that PATH has been supporting a minimal amount of work on this project to date with funding from another source. USAID funding for this project started October 1, 2004.

[1] Best practices page. Maternal and neonatal health website. Available at: http://www.mnh.jhpiego.org/best/pphactmng.asp. Accessed April 27, 2005.
[2] Mother-baby package: Implementing safe motherhood in countries. WHO/FHE/MSM/94.11, Geneva, 1994.
[3] Uniject is a trademark of BD.

Status of Project as of September 2005

The project is again in an active technical development phase, with the PATH team and staff from the Instituto Biologico Argentino SAIC (BIOL) working very closely to conduct preliminary studies and plan for the more extensive formal stability studies expected to begin in December 2005. Unless there are very unexpected results from these studies, BIOL should be able to provide initial supplies of oxytocin-Uniject for field study use by mid-2006.

Milestones expected in the past six months	Achievements and progress towards milestones
Complete broad landscape assessment of suppliers of oxytocin for injection as a finished dosage product.	Assessment 60 percent completed as of September 2005. Recently began further data collection on suppliers in collaboration with WHO, which has tasked some of its country/regional offices to conduct local assessments.
Initiate technical collaboration with BIOL on stability studies of their oxytocin-Uniject.	Oxytocin-Uniject screening and compatibility study initiated in late August at BIOL. Subcontract with BIOL signed early October 2005.
Participate in the POPPHI uterotonic supplies working group.	Continuing. HealthTech Uniject team leader, Steve Brooke, to chair working group meeting in early December 2005.

Problems encountered	Actions taken or plans to resolve
None.	

Milestones expected in the next six months (under HealthTech funding)	Planned activities to reach those milestones
Initiation of formal compatibility/stability testing (accelerated and real-time, per ICH guidelines) by mid-December 2005.	Preparations underway in cooperation with BIOL. PATH will contract MR Pharma to fill the Uniject batches for BIOL.
If accelerated aging data from formal compatibility/stability study results are positive at 3-month study timepoint (March 2006), confirmation of availability of oxytocin-Uniject for use in field trials under controlled conditions.	Ongoing monitoring and oversight of BIOL. Collaborative analysis of results and verification of regulatory requirements related to export for research use. Any update(s) on availability would be communicated to POPPHI partners.
Complete broad landscape assessment of suppliers of oxytocin for injection as a finished dosage product.	Ongoing work by PATH now benefiting from input which will come from WHO regional/country offices.

Strategic Objective 3

Cold Chain Technologies

Health Need Addressed

Improperly maintained or outdated refrigeration equipment, poor compliance with cold chain procedures, inadequate monitoring, and poor understanding of the dangers of vaccine freezing contribute to the weakness of the current vaccine cold chain. Emphasis has long been placed on keeping vaccines cold, with less attention devoted to prevention of vaccine damage from freezing. Published reports and field evidence generated under HealthTech support anecdotal reports and demonstrate that accidental freezing of vaccines in the cold chain is commonplace, potentially resulting in widespread delivery of vaccines whose potency has been compromised.

HealthTech IV Solution and Potential Impact

Cold chain technologies, such as the vaccine vial monitor, new refrigeration technologies, and new vaccine presentations strengthen immunization programs' ability to provide outreach services, improve the reliability of vaccine storage and transport, and reduce unnecessary wastage of valuable vaccines. Most importantly, these technologies will reduce the delivery of ineffective vaccines. Supported by the USAID-funded HealthTech program, and in collaboration with other organizations, PATH is addressing these priorities. Efforts include fostering changes in cold chain policies and an improved global awareness of the magnitude of accidental vaccine freezing. Evaluation and development is directed toward new technologies that improve vaccine storage and transport, prevent accidental freezing, and increase cold chain capacity for important new vaccines and presentations.

Ultimate Goals and Objectives of HealthTech Project

- Increase awareness of the extent and consequences of inadvertent vaccine freezing.
- Build global policy supporting freeze prevention.
- Facilitate development of new freeze-proof cold chain equipment.

Status of Project as of September 2005

The Cold Chain Technologies team continues to promote prevention of freezing of vaccines in the vaccine cold chain at international United Nations Children's Fund/World Health Organization (UNICEF/WHO) policy meetings. Working with ministries of health (MOH) in Bolivia, Indonesia, Mozambique, and Vietnam, PATH is modeling successful cold chain interventions designed to prevent freezing of vaccines. Requests for technical assistance with implementation of the WHO freeze assessment protocol demonstrate both increased concern about freezing of vaccines as well as awareness of HealthTech experience and expertise in prevention of freezing of vaccines.

Changes to cold chain equipment design are part of the solution to vaccine freezing, and the Cold Chain Technologies team is participating in the WHO Performance, Quality, and Safety Project (PQS) to improve cold chain equipment and introduce specifications for freeze prevention. Work with equipment manufacturers will include redesign of existing cold chain technologies (SolarChill, Twinbird), field evaluation of technologies (SolarChill), as well as guidance to the public-sector immunization market about purchase of cold chain equipment. An in-depth market analysis, informed by interviews with both end users and manufacturers, has recently been published to support the development and introduction of new technologies.

Milestones expected in the past six months	Achievements and progress towards milestones
Finalize WHO policy to prevent vaccine freezing.	PATH rewrote draft policy which is currently in the WHO policy and document review system. PATH-initiated components include the need for cold chain temperature monitoring studies, use of chilled water packs for vaccine transport, options for vaccine transport at ambient temperatures, and guidelines for operating and loading refrigerators to prevent freezing.
Finalize WHO protocol on assessing temperatures in the vaccine cold chain (based on PATH's protocol).	Complete. The protocol is posted on the WHO website available at: http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.01.pdf.
Finalize PQS specifications for freeze-proof refrigerators.	Underway. PATH continues to focus the discussion on freeze-prevention specifications.
Complete temperature monitoring study in Bolivia (with cofunding from UNICEF).	Study complete. Report being finalized. Results showed freezing temperatures in all shipments regardless of climate or elevation.
Establish new procedures in Mozambique to reduce freezing, supported by cofunding.	Agreement has been reached on a timeline (January 2006) for PATH to design a cold chain training curriculum and oversee its implementation in Cabo del Gado province.
Assistance to manufacturers with the development, refinement, approval, and introduction of improved cold chain equipment.	Redesign of SolarChill underway. Testing of a redesigned Twinbird refrigerator underway.

Milestones expected in the past six months	Achievements and progress towards milestones
Publish paper presenting a literature review of global evidence of vaccine freezing in the cold chain.	Underway.
Publish a cold chain equipment market study based on interviews with equipment manufacturers and purchasers.	Completed and published on TechNet. It provides a review of the public health cold chain equipment market and describes future trends such as the need for improved cold chain equipment with a freeze prevention design.

Problems encountered	Actions taken or plans to resolve
WHO cold chain policy and PQS process behind schedule.	PATH remains active in discussions and resolution of issues. Internal WHO processes take time and persistence.
Contractor hired to do redesign of the SolarChill behind schedule.	Continued interaction with contractor and SolarChill partners.

Milestones expected in the next six months	Planned activities to reach those milestones
Publication of a literature review of prevalence of vaccine cold chain freezing in developing countries.	Analysis complete. Writing underway.
Publication of Bolivia cold chain study results.	Study complete. Report underway; manuscript writing planned for fall 2005.
Validation of Twinbird redesign.	Testing in PATH laboratory through December 2005.
WHO prequalification of Twinbird design.	Completion of PATH testing.
Finalization of PQS specifications for refrigerators with freeze-prevention requirements.	PATH involvement in working group.
Completion of redesign of battery-less SolarChill technology.	PATH overseeing contractor and working with SolarChill partners.
WHO prequalification of SolarChill redesign.	Completion of PATH redesign and testing. PATH participation in PQS working group to finalize specifications for battery-less solar design.

Milestones expected in the next six months	Planned activities to reach those milestones
Publication of WHO policy on freeze prevention.	PATH will continue to interact with WHO to push for faster review. PATH will continue to provide WHO with freeze study results showing the prevalence of freezing.
Training of MOH personnel in one province of Mozambique on freeze prevention practices.	PATH developing training curriculum and will lead training in Mozambique.

Sharps Disposal Technologies

Health Need Addressed

Each year, more than 16 billion injections are administered worldwide. In some regions, 17 to 75 percent are estimated to be with reused, unsterilized injection equipment.[1] Unsafe reuse has been estimated to cause 20 million hepatitis B infections, 2 million hepatitis C infections, and 250,000 HIV infections annually.[2] The main tool to prevent reuse of unsterile syringes and needles is use of autodisable and safety needles and syringes. However, most syringes currently in use do not prevent reuse. Appropriate management of sharps and syringe waste play a critical role in safe injection by disabling syringes to prevent reuse, facilitating the safe and immediate disposal of contaminated sharps, reducing infectious waste volume, and facilitating ultimate disposal.

Safe injection is impaired by the lack of policies on proper disposal of sharps, appropriate equipment, and evidence of cost-effective systems. Currently, sharps waste is dangerous to the community and health care workers; and waste handlers are not protected from hazardous sharps when collecting, storing, transporting or disposing of sharps waste.[3,4,5]

HealthTech IV Solution and Potential Impact

The use of needle removers to separate the needle from the syringe immediately after use reduces the risk of potential infection to patients, health care workers, waste handlers, and the community by:

- Immediately isolating the contaminated sharp.
- Preventing syringe and needle reuse (since the needle remover also destroys the syringe).
- Reducing needle-stick injury risk for waste handlers and scavengers.

By separating the sharp from the syringe, waste disposal systems are more effective and efficient. They:

- Provide an immediate option for sharps disposal via protected needle pits.
- Heighten awareness of contaminated sharps by creating behavioral practices specific to contaminated needle waste management.

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[1] Hutin Y, Hauri A, Armstrong G. Use of injections in healthcare settings worldwide, 2000: Literature review and regional estimates. *British Medical Journal*. 8 November 2003;327(7423):1075.

[2] Hutin Y, Hauri A, Chiarello L, et al. Best infection control practices for intradermal, subcutaneous, and intramuscular needle injections. *Bulletin of the World Health Organization*. 2003;81(7):491-50.

[3] Jie L. Rapid Assessment of Injection Practices in China, Final Report to the Ministry of Health of China and the Secretariat of SIGN, December 2002.

[4] Dicko M, Oni AQ, Ganivet S, et al. Safety of immunization injections in Africa: Not simply a problem of logistics. *Bulletin of the World Health Organization*. 2000;78(2):163–169.

[5] Rajasekara M, Sivagnanam G, Thirumalailolundusubramainan P, et al. Injection practices in southern part of India. *Public Health.* 2003;117:208–231.

- Reduce disposal costs by decreasing or eliminating the requirements for transport and safety boxes.

Taking into account developing-country injections, reuse, needle-stick injury, and infections caused by reuse, we have estimated that needle-removal devices could, by 2013:

- Avert more than 9 million hepatitis B, hepatitis C, and HIV infections over a ten-year period (based on an assumption of 20 percent adoption of needle-remover devices by 2013 globally).
- Reduce the overall systems cost of injections (including treatment for inadvertent infection caused by unsafe injection) by more than US$70 million.
- Reduce the cost per safe injection from US$0.077 to US$0.065 over ten years.

Ultimate Goals and Objectives of HealthTech Project

The project goal is to advance, test, and introduce safe needle-removal and sharps disposal systems for health centers and outreach services. The objectives are to:

- Determine the status of point-of-care needle-remover systems.
- Optimize needle-remover systems for use in developing-world health centers and outreach services.
- Validate needle-remover systems in developing-world settings.
- Align global and national policies to accommodate needle-remover use.
- Introduce needle-remover systems into practice.
- Evaluate and refine needle-remover and syringe-disposal systems.

Status of Project as of September 2005

The team has just completed needle-remover studies in Uganda and Senegal, while the World Health Organization (WHO) has completed studies in Madagascar and Burma. Together these studies greatly broaden evidence of the safety and usefulness of needle removers. PATH has adapted and is preparing to evaluate a lower-cost device, a popper and scissors fitting that will convert locally available containers into needle removers.

BD Hub Cutter in use.

Milestones expected in the past six months	Achievements and progress towards milestones
Go/no go decision about field trial for low cost needle remover (Hopkins) device.	100 prototypes made for field trial and potential sites and collaborators are being contacted.
Disseminate results of BD Hub Cutter evaluation of acceptability, fit, and function of the cutter in use in family-planning settings in Uganda.	Stakeholders meeting held and recommendations about device given to manufacturer. Final report sent to funders and in-country participants. The Hub Cutter was quickly accepted by study participants who reported that it was extremely dependable, easy to use, and increased the overall cleanliness of their facilities. The cutter reduced volumes of clinical waste by about 35 percent and allowed health workers to consider using infectious waste bags for syringe barrels. The main concerns with the cutter were final disposal and incompatibility with some needle sizes. Although there were clear advantages, the cutter is not likely to be of sufficient benefit if introduced as part of one vertical program (such as family planning only). The device's unique features may be of greater benefit as part of outreach efforts or in remote, rural settings.
Disseminate results of Senegal evaluation of acceptability of needle remover and sharps barrel.	Report posted on TechNet. The study found that health workers preferred needle removal over putting the complete needle and syringe into the safety box. Another advantage was reduction in the number of safety boxes needed, since 50 percent more defanged syringes fit into a safety box than syringes with needles. The study also validated the use of the needle barrel in areas where needle pits are not appropriate or acceptable. The barrel provides a good option in areas where high water table, rocky ground, or the lack of open ground prevents the digging of pits.

Milestones expected in the past six months	Achievements and progress towards milestones
Document infection risks of used syringes (without needles).	Literature reviewed, though little existing research on the topic was found. Will proceed to initiate global dialogue about infectious risk.

Problems encountered	Actions taken or plans to resolve
Delays in bringing the Demolizer technology (non-incineration disposal alternative) to PATH for evaluation,	Meeting with key stakeholders on Demolizer technology now scheduled at PATH in late November. Test protocol to be developed.
Technical problems continue with the solar melter being tested by IT Power. Also, there are questions as to whether something as big and complex as this device can be useful in low-resource health center setting.	Field testing of refined solar tester will take place in small steps to evaluate feasibility carefully. Will start with only one to two sites.
Difficulty finding published scientific rationale to help settle the question of how defanged syringes should be disposed.	Will continue to seek data and advice about defanged syringe disposal. May start dialogue through TechNet.
There has been a delay in disseminating the research from the 2003 India needle-remover study.	PATH has just gotten word in October 2005 that the manuscript has been accepted by *Tropical Doctor* for publication. No publish date available yet.

Milestones expected in the next six months	Planned activities to reach those milestones
Initiate trial of Hopkins popper and scissors.	Finalize sites and protocol. Train participants and data collectors.
WHO Performance, Quality and Safety Project (PQS) specifications for needle removers.	As working group member, push process forward.
Conduct lab testing, design refinement, and field testing of an electric syringe melter.	Meeting to be held with collaborators in November to develop protocol. Lab testing planned for December 2005.
Complete an analysis of the risks of defanged syringes.	Continue to carry out literature review.

Milestones expected in the next six months	Planned activities to reach those milestones
Identify manufacturer of non incineration treatment technology interested in simplifying their equipment for developing-country use.	Research existing technologies and manufacturers.
With co-funding, design and begin a field investigation of the use of retractable syringes in an immunization program, . Retractable needles will offer the benefit of simplification of the process of disposal because the needle is contained already automatically. Alternative disposal methods of contained needles will be explored and may result in more options for disposal of sharps (i.e., plastic bags instead of safety box).	Protocol development, site identification, collaboration with local partners, implementation, and monitoring.

Gentamicin in the Uniject Device

Health Need Addressed

The World Health Organization (WHO) estimates that at least 4 million neonatal deaths (i.e., death during the first 28 days of life) occur around the world every year. Severe bacterial infections are major contributors of newborn morbidity and mortality. In the developing world each year, an estimated 30 million children develop an infection during the neonatal period, and infectious diseases account for over one-third of all neonatal deaths. In 2000, a WHO advisory committee recommended intramuscular injections of ampicillin and gentamicin as the standard therapy for these bacterial infections and the treatment of neonatal septicemia, meningitis, and pneumonia. Case-fatality rates for severe bacterial infections are high in part due to not administering or delaying the administration of necessary antibiotics. Therefore, it is important that newborns with these infections receive immediate treatment, even before the infectious agent is known. When neonatal infections occur, many deaths can be avoided if the signs are recognized early and the disease is treated promptly.

HealthTech IV Solution and Potential Impact

To improve neonatal survival from infectious diseases, Uniject™[1] injection devices prefilled with a single dose of gentamicin (hereafter called "gentamicin-Uniject") could be easily transported and used in a home setting with an oral antibiotic when the signs of a neonatal infection are first detected. Community-based health workers could be trained to use the gentamicin-Uniject device and a complementary oral antibiotic in order to extend the accessibility and facilitate the administration of antibiotics for early treatment of neonatal infections. Furthermore, gentamicin-Uniject devices could potentially be incorporated into the revised integrated management of childhood illness guidelines, which have been adapted for acute management of common infectious neonatal illnesses. If gentamicin-Uniject is used safely, properly, and efficiently for infants with severe bacterial infections, the Uniject device could make a significant contribution to reducing neonatal mortality in developing countries. HealthTech has recently allocated funds for further development of this application of the Uniject device, with cofunding provided by the Bill & Melinda Gates Foundation.

Ultimate Goals and Objectives of HealthTech Project

Create a sustainable, commercial supply of gentamicin-Uniject so this innovative combination can be fully evaluated for treatment of neonatal infections.

[1] Uniject is a trademark of BD.

Status of Project as of September 2005

After a period of building the appropriate industry partnerships to move the project forward over the past few months, significant technical work has been initiated. This comprehensive set of screening studies should provide a clear indication of compatibility of various buffering systems and gentamicin raw materials in the Uniject device by the end of 2005.

Milestones expected in the past six months	Achievements and progress towards milestones
Collaboration agreement with Instituto Biologico Argentino SAIC (BIOL) completed.	Subagreement with BIOL signed (in early October 2005).
Protocol and preparation for screening and compatibility study completed.	Completed on schedule in August. Study scope expanded based on the number of buffering systems and gentamicin active pharmaceutical ingredient (API) combinations to be evaluated.
Screening and compatibility study initiated.	Study initiated in early September 2005 with 12 formulation/API combinations; 3 more will be initiated in November 2005, using an API that has proven difficult to obtain. Consultant traveled to Argentina to help the BIOL team launch the expanded scope study on schedule.
Interim results of screening and compatibility study available.	Preliminary interim data (at the 6-week mark in mid-October 2005) appears promising for 2 of 3 buffering systems under evaluation. *Full analysis is pending.*

Problems encountered	Actions taken or plans to resolve
Additional time was required to obtain gentamicin API from Sandoz/Lek, 1 of the 4 manufacturing sources selected by the team. The company's practices do not allow much flexibility in terms of distributing sample material for analysis.	Screening and compatibility of formulations containing the Sandoz/Lek gentamicin API will start late, in November 2005. Since the Sandoz/Lek product will not be available in sufficient quantity for the targeted December 2005 start of a formal stability study, any such study would not start until March 2006. This should not delay the overall project since it is unlikely API material from the other 3 sources will prove substantially inferior or incompatible.

Milestones expected in the next six months	Planned activities to reach those milestones
Screening and compatibility study completed.	Ongoing monitoring and oversight of BIOL.
Frontage Laboratories' analysis of gentamicin API from 4 different sources completed and results compared with the relevant formulations' performance in the screening and compatibility study.	Ongoing monitoring and oversight of Frontage Laboratories. BIOL and PATH will analyze and compare results with those from screening and compatibility study.
Protocol and preparation for formal stability study completed.	In collaboration with BIOL, will fully specify and plan the batch production and QA/QC processes involved, data collection procedures and instruments, and new equipment qualifications. PATH will contract MR Pharma to fill the study formulation(s) into Uniject on behalf of BIOL, in accordance with BIOL QA/QC and regulatory needs. PATH technical personnel may travel to Argentina to assist in finalizing preparations.
Formal stability study initiated with selected formulation(s).	Study initiation targeted for mid-December 2005. If unexpected problems delay initiation, then initiation would be delayed to early March 2006. (As noted above, any selected formulation containing Sandoz/Lek API will be delayed until early March 2006 by default.)

Evaluation of Neonatal Resuscitators

Health Need Addressed

Birth asphyxia refers to a baby who does not breathe at birth and is estimated to account for one-third of the estimated 4 million neonatal deaths that occur annually.[1] This results in over 1 million neonatal deaths and an unknown number with long-term neurological disability. Over two-thirds of neonatal deaths and about 40 percent of infant deaths occur in the first week of life; birth asphyxia is a major cause of death in the same time period. Limited data suggest that deaths due to birth asphyxia have remained relatively unchanged in developing countries.[2]

HealthTech IV Solution and Potential Impact

The key to reducing death due to birth asphyxia is the provision of appropriate care to underserved populations during delivery. Appropriate care for birth asphyxia requires that neonatal resuscitation skills and appropriate technology must be made available to all skilled birth attendants and to community-level workers where skilled attendants are not available. A neonatal resuscitator is a critical part of the equipment needed for proper and effective resuscitation.

A neonatal resuscitator that is affordable and easy to use, clean, and store could increase the user availability and use of such lifesaving devices in the developing world. The estimated potential impact could be up to 1 million neonatal deaths averted annually.

Field guide produced September 2005.

Ultimate Goals and Objectives of HealthTech Project

To increase understanding and awareness of neonatal resuscitator device performance among the international community and to enhance availability of appropriate devices in low-resource settings, particularly in Asia and Africa, by:

- Disseminating findings from a recent study about the context of use and related user needs of neonatal resuscitators in developing countries to appropriate audiences (i.e., policymakers and public health professionals working with neonates in developing countries).

[1] WHO. Perinatal and Neonatal Mortality: Global, Regional and Country Estimates. 2001.
[2] Saving Newborn Lives. Birth Asphyxia: Report of a Meeting, Cape Town, South Africa 29 November to 2 December, 2002.

- Planning and implementing a technical meeting to present results of evaluations of devices to a group of neonatal experts and fostering discussion about device performance and possible requirement specifications.
- Increasing availability of neonatal resuscitator devices in Asia and Africa by providing technical assistance to producers to adapt and improve devices manufactured in low-resource settings.

Status of Project as of September 2005

- PATH recently completed a three-part evaluation of neonatal resuscitators incorporating a context of use survey, as well as laboratory and user evaluations of commercially available resuscitators.
- To summarize the findings from these evaluations, PATH authored a detailed report and a pamphlet-style comparative guide to the resuscitators evaluated entitled *Practical selection of neonatal resuscitators, A field guide*.

Milestones expected in the past six months	Achievements and progress towards milestones
Complete context of use and user needs survey.	Online survey completed by cohort of international experts and birth attendants. Main findings indicated a preference for bag and mask resuscitators, and the important features cited for resuscitators included ease of use, size of mask, and overall function.
Complete laboratory and user evaluations of a selection of neonatal resuscitators.	Evaluation, including laboratory-based data and skilled and unskilled user evaluations, completed in August 2005. User evaluations demonstrated the usability of different device designs and highlighted differences between tube and mask and bag and mask resuscitators. Outcomes included important specific device features that are recommended irrespective of device type.
Complete report on both context of use and user evaluations to USAID.	Report completed and submitted in September 2005.
Completion of comparative assessment guide to resuscitators appropriate for program use.	*Practical selection of neonatal resuscitators, A field guide*, comparing 11 resuscitators, completed in September 2005. The guide will be useful to program managers and health workers making procurement decisions.

Milestones expected in the past six months	Achievements and progress towards milestones
Submission of abstracts for survey and user/laboratory evaluations to Global Health Council meeting.	Abstracts submitted for both evaluations October 2005.

Problems encountered	Actions taken or plans to resolve
Because of the high number of resuscitation devices available on the global market and the limited amount of funding for conducting an evaluation, HealthTech had to limit the number of devices reviewed.	Limited number of resuscitators selected for initial evaluation. Complete global inventory of available resuscitators is planned for 2006.

Milestones expected in the next six months	Planned activities to reach those milestones
Submit manuscript on evaluation to peer-reviewed journal.	Appropriate journal(s) for submission will be identified in November 2005. Manuscript will be drafted and submitted in November/December 2005.
Present at Global Health Council if abstracts are accepted.	Develop presentation with content appropriate for general audience.
Facilitate technical meeting on neonatal resuscitators.	Identify meeting participants and venue in November/December 2005. Develop agenda to include discussion and consensus on performance requirements for neonatal resuscitators and utility of WHO prequalification of devices. Conduct meeting planned for January 2006. Report on meeting outcomes to USAID in early 2006.
Initiate provision of technical assistance to resuscitator manufacturers in Asia and Africa.	Develop global inventory of available neonatal resuscitation devices by January 2006. Identify Asian firms interested in limited technical assistance in first half of 2006. Conduct market assessment of existing and/or redesigned devices in select African countries by June 2006.

Retinol Binding Protein Enzyme Immunoassay

Health Need Addressed

Micronutrient malnutrition has emerged as one of the greatest public health concerns in the world today. Almost one-third of children in developing countries are affected to some degree by vitamin A deficiency (VAD), which impairs their growth, development, vision, and immune function (including resistance to disease), and in extreme cases leads to blindness and death.[1,2,3]

A body of knowledge and experience exists that effectively addresses VAD through both short-term and long-term interventions. Global efforts have promoted capsule supplementation, food fortification, nutrition education, and the so-called food-based strategies to combat VAD. However, the targeting and implementation of effective interventions requires accurate and timely data. Generating information on VAD at a country and subnational level has been hampered by technology constraints. The lack of affordable, valid, and reliable screening methods has made it difficult and expensive to conduct badly needed vitamin A assessments. The development and introduction of the retinol binding protein-enzyme immunoassay (RBP-EIA) to assess VAD alleviates this constraint by generating prevalence data and information to promote the planning, implementation, and evaluation of vitamin A interventions to improve child health and nutrition.

HealthTech IV Solution and Potential Impact

The RBP-EIA is a competitive assay, which detects and quantifies retinol binding protein in human serum. The test uses purified human RBP adsorbed to microtest strip wells to compete with natural RBP found in serum. The test results for 96 determinations are available in as few as 35 to 40 minutes after the start of the assay; however, it is strongly recommended that all samples, including calibrators, be performed in duplicate. Therefore, the kit provides a total of 48 results. The RBP-EIA is designed to access and monitor the vitamin A status in populations. While the results for the assay are quantitative, it should not be considered a diagnostic test for detection of VAD in individual patients but rather as a research and epidemiological surveillance tool to be used at a population level.

This technology addresses USAID's strategic objective to increase the use of key child health and nutrition interventions (SO 3). It does this by improving the quality and availability of key screening services (IR 3.4); improving preventive behaviors related to child health and

[1] UN ACC/SCN (United Nations Administrative Committee on Coordination/Subcommittee on Nutrition). *Third Rreport on the World Nutrition Situation.* Geneva:ACC/SCN; 1997.

[2] World Health Organization, *Global prevalence of vitamin A deficiency: Micronutrient deficiency information system. WHO MDIS Working paper #2.* Geneva:WHO; 1995.

[3] Sommer A, West KP. *Vitamin A deficiency: Health, survival, and vision.* New York, NY, and Oxford, UK: Oxford University Press; 1996.

nutrition (IR 3.3); and providing information to improve policies and increase global, national, and local resources for appropriate child health interventions (IR 3.2).

The RBP-EIA offers a rapid, inexpensive, and quantitative tool for determining vitamin A status at the population level. Vitamin A status is currently being determined by "gold standard" high-performance liquid chromatography (HPLC) methodologies that are expensive and require significant investments in training and time to carry out. The RBP-EIA test developed at PATH is simple and requires a relatively small amount of specimen. It reduces reliance on centralized laboratory facilities in developing countries and saves time and money by eliminating the need to transport specimens to a developed country for analysis using overly sophisticated and costly tests such as HPLC. It provides a more cost-effective tool for the monitoring and recognition of VAD in targeted populations, will assist surveillance units in the field with the assessment of VAD status at the population level, and reduces the time between assessment and implementation of interventions to address VAD. We expect that the RBP-EIA will facilitate the ease of conducting vitamin A field assessments and increase the number of countries that conduct prevalence surveys to assess VAD, especially in countries where they have not yet been performed but where the need may be the greatest.

Ultimate Goals and Objectives of HealthTech Project

The goal of the project is to enhance the reliability and ease of VAD assessment and decrease the associated cost. The objectives are to:

- Improve the consistency of the results of vitamin A assessment, including ease of specimen analysis and interpretation.
- Improve the reliability of VAD estimates.

Status of Project as of September 2005

The RBP-EIA is poised for introduction into the public health arena in 2006. Scimedx, the private-sector licensee, is now able to manufacture the RBP-EIA with three to four weeks notice. To ensure demand for the test, there is continued need for PATH to introduce the test to potential users and complete the activities that are currently underway with the United Nations Children's Fund (UNICEF) in Myanmar, the Centers for Disease Control and Prevention (CDC), and Demographic and Health Surveys (DHS) in Uganda.

As the project moves from PATH introduction to open access, additional support to procurement officers to select the RBP-EIA will be essential. This will require some assistance to Scimedx to develop appropriate materials for procurement and logistic officers at organizations like UNICEF, World Health Organization (WHO), and USAID projects.

Milestones expected in the past six months	Achievements and progress towards milestones
Senegal sample analysis for retinol to be completed by CDC as a result of multiple problems with the original retinol analysis. Complete analysis of the RBP from serum collected for a micronutrient intervention conducted in Senegal in conjunction with University of California at Davis, the University of Dakar, and the Micronutrient Initiative.	Data analysis completed. Summary of Evidence document is completed. The summary compiles evidence of the performance of the RBP-EIA compared to retinol using different sample types that have been conducted over the past 5 years. The data support the use of RBP-EIA as an alternative measure for VAD, compared to retinol analyzed using HPLC. Final reports expected by December 2005.
Job aids developed and field-tested in support of field use of the RBP-EIA. End-user feedback obtained and incorporated into the RBP-EIA and supporting materials.	Training materials were tested in Myanmar. Revised job aids based on the feedback are expected to be done by December 2005.
Candidate “early adopters” to be selected and provided with RBP-EIA tests and Q&A technical support at no cost to gain exposure for the test, build a market, and demonstrate the technology.	Three test kits distributed to CDC for them to use the test in house. CDC has delayed their analysis of VAD from Papua New Guinea due to organizational changes at CDC. The Mali country survey was cancelled. UNICEF Myanmar purchased 4 test kits to evaluate in country. They are expected to place an order for 36 kits for analysis of VAD. End-user survey data analyzed as part of label review. End users gave the RBP-EIA test high marks for ease of use and made useful suggestions for making the product insert clearer. The RBP-EIA product insert was revised and finalized based on end-user feedback.
RBP-EIA introduced to key stakeholders and the broader consumer audience.	Not completed yet.

Problems encountered	Actions taken or plans to resolve
Delays in introducing RBP-EIA to key stakeholders and the broader consumer audience.	These meetings have not been organized yet, given the departure of Deborah Lans and difficulty in finding a time that meets all parties' schedules.

Milestones expected in the next six months	Planned activities to reach those milestones
Final report on analysis of Senegal samples.	Final report expected by December 2005.
Job aids developed and field-tested in support of field use of the RBP-EIA. End-user feedback obtained and incorporated into the RBP-EIA and supporting materials.	Revise job aids and get end-user feedback from UNICEF Myanmar and other potential users. Proceed with finalizing job aids.
Continued work with candidate "early adopters."	Collaborate with Macro International to introduce RBP-EIA in DHS Uganda in 2006. Identify options through USAID's A2Z micronutrient program for use in the field.
Interact with Scimedx to ensure that the RBP-EIA is commercially available in 2005 and 2006 by monitoring quality, introducing Scimedx to potential users, and jointly supporting promotional opportunities.	Organize introductions via planned meetings to stakeholders at Johns Hopkins University; at USAID; USAID's micrantrient program–A2Z; and at UNICEF in NY.
Address any user or technical issues with performing the RBP-EIA as a result of increased access and use of the RBP-EIA in developing-country settings. Facilitation of procurement of test by others.	Demonstrate the use of the RBP-EIA using dried blood spots through collaboration with DHS Uganda and supporting documents. Develop a comparison document that allows procurement officers to easily review the features and benefits of commercially available test kits for RBP-EIA and make informed decisions. Develop a sole-source document with Scimedx to facilitate the procurement of RBP-EIA test.

Strategic Objective 4

Immunochromatographic Strip Test for Chlamydia

Health Need Addressed

Accurate diagnosis and control of sexually transmitted infections continue to be challenges for health care providers in many developing countries. Although there are many simple and rapid tests available for the diagnosis of *Chlamydia trachomatis* (CT) infection, the sensitivity of many are low, and most, if not all, are too expensive for use in developing countries. The development of a rapid immunochromatographic strip (ICS) test for chlamydia that is sufficiently sensitive, specific, rapid, and affordable would be an extremely valuable tool.

HealthTech IV Solution and Potential Impact

The ICS test for chlamydia, developed under HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify a chlamydia-specific antigen obtained directly from clinical specimens. The strips are stable at ambient temperatures if packaged appropriately. This simple, rapid test will allow testing to be performed on direct clinical specimens from patients at the point of care in rural or smaller clinics, hospitals in the developing world, or other resource-limited settings. Results can be returned within one hour, thereby allowing effective patient follow-up, additional counseling, and the prescribing of appropriate therapeutic drugs if needed. Epidemiological surveillance teams in the field may also use the test to gather baseline data or to assess the effect of public health interventions.

Ultimate Goals and Objectives of HealthTech Project

- Commercial availability of rapid chlamydia test for use in developing countries.
- Published data supporting the utility of this test in the developing world.
- Endorsement of the test by the World Health Organization.

Status of Project as of September 2005

The CT ICS test prototype has been developed and optimized and is being evaluated in a large field evaluation in Bolivia. Discussions with manufacturers about collaborative co-development and technology transfer of this test are underway. Finally, we are in contact with individuals at Emory University and the Global Network for Perinatal and Reproductive Health about conducting introduction and evaluation studies in South Africa and Colombia respectively.

PATH staff training technicians in Bolivia.

Milestones expected in the past six months	Achievements and progress towards milestones
Preliminary results from a field evaluation of the test in Bolivia.	Preliminary arrangements have been made. Although field trial was delayed from the original date due to political instability in Bolivia, the training and systems were put in place during field trips in August.
Technology transfer to a commercial manufacturer in the developing world.	Final transfer is pending due to legal negotiations. However, significant progress has been made toward an agreement that involves a collaborative codevelopment with a potential licensee.
Identification of a second technology transfer recipient, preferably in South America.	Two potential technology transfer candidates have been identified—one in Brazil and the other in Vietnam. Productive preliminary discussions with the entity in Vietnam are underway.

Problems encountered	Actions taken or plans to resolve
The field trial in Bolivia was delayed due to political unrest in La Paz.	Field evaluation preparation work until the change in political leadership took place in August. Field trial now successfully underway.

Milestones expected in the next six months	Planned activities to reach those milestones
Complete data from field trial of over 1,500 women in Bolivia.	Collaboration with Population Council in data collection at four sites throughout the country is underway. Formal agreements have been signed, field staff have been trained, and supplies are on the ground. IRB submissions have been reviewed and final revisions are being made before approval is granted. The trial is expected to take 9 months and will be completed by August 2006.
Decision point reached on the feasibility of a Europium latex lateral flow detection system for CT. This could potentially enhance the signal of the test making it easier for the user to interpret, therefore, substantially increasing the test's sensitivity.	Experiments to understand the threshold of detection of the Eu-Latex system. Comparison of this threshold to the detection threshold of the traditional colloidal gold system. Optimization of buffers and signal reagents.
Planning for an introduction study either in Colombia or South Africa.	Discussions with Jorge Tolosa about the Colombia field site and Ralph DiClemente about the South Africa field site.

Microbicides Applicator Evaluation

Health Need Addressed

AIDS is the leading cause of mortality among adults aged 15 to 59 years.[1] Women are increasingly bearing the disproportionate burden of the AIDS epidemic. In 2003, women accounted for nearly 50 percent of all people living with HIV, compared to 41 percent in 1997.[2] In Africa, women are 1.3 times more likely than men to be infected with HIV; young women aged 15 to 24 are 2.5 times more likely to be infected than young men.[3]

Due to social norms, gender inequalities, and economic disparities, women are often unable to protect themselves from HIV through abstinence, mutual monogamy, or male condom use. Safe, effective microbicides could provide urgently needed options for women and men seeking protection from HIV and other sexually transmitted infections.

With over 30 potential microbicides in preclinical or clinical trials, most research has focused on the gels/creams intended for topical application, with much less targeted research on the devices (applicators) that will be used to deliver the microbicides. The applicator devices will be critical in ensuring a safe, effective microbicide product. The applicator impacts the overall product's safety (relationship with product purity and stability, avoidance of local trauma associated with insertion or use), efficacy (consistent delivery of the required amount of product in the intended location), and acceptability (comfort, ease of use, disposability). Acceptability of the applicator, in addition to the microbicide, will greatly impact whether the product is used consistently and correctly. From past female condom research,[4] it is clear that user acceptability, in addition to product cost, is a major determinant of product uptake and actual use. Finally, the design of a product for worldwide users estimated at 34 to 88 million women per year[5] has a potential environmental impact in terms of waste disposal.

HealthTech IV Solution and Potential Impact

Modeling efforts have shown that a partially effective microbicide could avert over 2.3 million cases of HIV in three years, given certain levels of uptake, coverage, and use.[6] As noted above, the applicator will play a critical role in product uptake and use. We have the opportunity to evaluate and address these important issues before microbicide product

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[1] World Health Organization. *Facts and Figures from The World Health Report 2003, Shaping the future*. Geneva:WHO; 2003.
[2] UNAIDS. *Report on the Global AIDS Epidemic*. UNAIDS; 2004.
[3] UNFPA. *State of the World Population.* UNFPA; 2004.
[4] Hoffman S, et al. The future of the female condom. *Perspectives on Sexual and Reproductive Health*. 2004;36(3):120–126.
[5] Pharmaco-Economics Working Group of the Microbicide Initiative. *The Economics of Microbicide Development: A Case for Investment.*
[6] Public Health Working Group of the Microbicide Initiative. *The Public Health Benefits of Microbicides in Low Resource Settings: Model Projections.*

introduction, so that appropriate applicators can be as accessible and acceptable as possible, leading to much greater levels of use-effectiveness and greater rates of HIV protection.

Ultimate Goals and Objectives of HealthTech Project

The goal of the project is to ensure that safe, appropriate, affordable applicators are available for use in low-resource settings at the time of microbicide introduction. The objectives of this project are to:

- Provide data that can inform product selection of devices for use in low-resource settings.
- Provide data on status and availability of existing applicators that meet cost, user, product, and manufacturing requirements.
- Strengthen linkages between applicator and microbicide researchers, developers, and sponsors to ensure timely and effective product introduction.

Status of Project as of September 2005

We have submitted a preinvestigational new drug (IND) packet to the US Food and Drug Administration (FDA) which outlines our proposed applicator bridging studies; we are currently waiting for the FDA to provide us a date for our teleconference with them. Based on the outcome of this meeting, we hope to initiate our main bridging study with collaborators at Profamilia in the Dominican Republic by January 2006. We anticipate that data from this study (using a cardboard applicator from Tekpak, Inc.), and other laboratory-based studies, can then be used by microbicide developers to switch from a prefilled applicator to a user-filled applicator in the course of their clinical trials or at the time of product introduction.

Milestones expected in the past six months	Achievements and progress towards milestones
Submit article on acceptability of applicators to *AIDS* for publication.	Article submitted and rejected by *AIDS*.
Participate in pre-IND meeting with FDA to discuss regulatory pathways for new applicators.	The pre-IND packet has been submitted to the FDA. We are waiting a meeting date from the FDA for the pre-IND teleconference. We expect this teleconference to occur before December 2005.
Conduct international scan for applicator manufacturers.	Scan has been completed in South Africa and India and identified several qualified applicator manufacturers with design, manufacturing, and business experience who could be considered for future microbicide introduction strategies.

Milestones expected in the past six months	Achievements and progress towards milestones
Convene microbicide meeting to discuss regulatory needs and research priorities for bridging current microbicide products with lower-cost, alternative applicators for product introduction.	This regulatory meeting has been postponed to early 2006 so that we can share the outcomes of the FDA discussion with meeting participants. In the meanwhile, we will give an update of PATH applicator activities, including our proposed bridging study concepts, at the Microbicide Cooperating Agencies meeting on November 9-10.

Problems encountered	Actions taken or plans to resolve
The process of completing the pre-IND packet took more time than anticipated.	Extensive discussions focused on whether it was most appropriate to submit our proposed study under a pre-spell out or pre-IND to the FDA. With guidance from Family Health International (FHI) and PATH regulatory personnel, we jointly decided to pursue the pre-IND route and finalized and submitted the packet in October 2005.
PATH encountered numerous scheduling conflicts while planning an applicator regulatory meeting to be held at the Microbicides 2006 Conference in Cape Town, South Africa (April 2006).	PATH originally proposed convening a separate meeting at Microbicides 2006 to discuss regulatory issues regarding applicators with donors, trial managers, researchers, and developers. A session on Applicator Regulatory Discussion is now on the agenda of the International Working Group for Microbicides meeting (April 2006) and we are hoping to confirm a space on the agenda of the South African Development Community meeting (April 2006). The participants in these two meetings represent the original group interested in the applicator meeting, as well as many additional stakeholders whose input will be useful for advancing applicator research and regulatory discussions.

Milestones expected in the next six months	Planned activities to reach those milestones
Acceptability study manuscript accepted for publication.	Submit manuscript to additional journals, beginning with *Sexually Transmitted Diseases*, October 2005.
Pre-IND teleconference with FDA.	Pre-IND packet submitted to FDA and we are waiting for notification of the meeting date.
Convene meeting in Washington, DC, to discuss regulatory needs and research priorities for bridging current microbicide products with lower-cost, alternative applicators for product introduction.	Assess potential dates with key participants, including personnel from FHI and USAID. Confirm date and send out invites to interested attendees. Convene meeting at the PATH DC office.
Initiation of applicator bridging study in the Dominican Republic.	Based on outcomes of FDA meeting, revise proposed study protocol as needed. Gain IRB approvals at PATH and Profamilia (study site in the Dominican Republic). Conduct researchers meeting prior to study initiation.
Initiation of laboratory-based study of applicator dose delivery at PATH.	Based on outcomes of FDA meeting, revise protocol as needed. Procure prefilled applicators from Heinke Technology Inc. Plastics (HTI) with placebo to provide comparison with user-filled applicators from Tekpak. Pretest protocol and revise as needed. Conduct testing at PATH.

Packaging Solutions to Improve Provision of Nevirapine in PMTCT Programs

Health Need Addressed

It is estimated that 2.2 million children under the age of 15 around the world are HIV positive, with some 560,000 becoming newly infected in the year 2004.[1] Clinical trials have shown single-dose nevirapine (NVP) to be an efficacious therapy for reducing mother-to-child transmission (MTCT) of HIV-1. The single-dose therapy includes a 200 mg NVP tablet (hereafter referred to as NVP tablet) to be taken by the mother at the onset of labor and a fixed dose of 0.6 ml of NVP oral suspension (hereafter referred to as NVP syrup) for the infant dose, to be given to the baby within 72 hours of birth.[2,3] Study results demonstrate that the NVP regimen is low cost, and when administered correctly, has the potential to cut HIV transmission by 50 percent.[4] However, administration of the infant dose in resource-limited settings can be challenging given the timing requirement for administration; the limited availability of health care services, including both antenatal care (ANC) and prevention of MTCT (PMTCT) services; and the high prevalence of home births.

Some programs provide HIV-positive pregnant women with the NVP tablet to take home and take at the onset of labor. The most common approach to date for provision of the NVP syrup has required women to either give birth in health facilities or come to a health facility within 72 hours of birth so the infant can be given the dose.

In some settings, PMTCT programs are beginning to prefill and package a fixed dose of 0.6 ml of NVP into oral-dosing syringes and provide these to HIV-positive pregnant women during ANC visits for future administration to their baby after delivery, either in a facility or at home. These current clinic-level packaging practices vary widely. During a recent field visit to Kenya, PATH staff observed PMTCT staff drawing 0.6 ml of NVP syrup into oral-dosing syringes and then using household tinfoil, thin plastic bags, sheet paper, and small cardboard boxes in various combinations to protect the syringe while in the HIV-positive woman's possession.

Provision of the NVP tablet at ANC visits for women to take home seems to have increased in prevalence in the last few years. However, provision of the infant-dose NVP syrup has

[1] UNAIDS. *AIDS Epidemic Update: December 2004*. 2004.

[2] Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*. 1999;354(9181):795–802.

[3] Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *Journal of Infectious Diseases*. 2003;187(5):725–735.

[4] World Health Organization. Coverage of Selected Health Services for HIV/AIDS Prevention and Care in Less Developed Countries in 2001. November 2002.

been slow to follow; the lack of single-dose packaging for NVP has been a critical barrier, often preventing provision to HIV-positive women at ANC visits.[5]

HealthTech IV Solution and Potential Impact

Overcoming the packaging challenges to increased coverage of at-risk newborns with the infant dose of NVP syrup has been the driving force behind the establishment of a public-private partnership among USAID, Boehringer Ingelheim (BI) (manufacturer of Viramune®[6] brand NVP), and PATH. PATH's proposed improvement to NVP syrup packaging is a medical grade, self-adhesive sealing (hereafter referred to as self-sealing) foil laminate pouch specifically shaped and sized for the NVP-filled, 1-ml Exacta-Med®[7] dispenser (the oral-dosing syringe currently being donated as part of BI's Viramune donation program).

When used with the NVP syrup and the Exacta-Med dispenser, the self-sealing foil pouch will:

- Create a packaging solution that can be implemented at the PMTCT clinic level without requirements for additional equipment or power resources.
- Improve ease of use for PMTCT clinic service providers and HIV-positive pregnant women.
- Provide increased protection for the infant dose after being transported and stored by the HIV-positive pregnant woman until after her delivery.
- Provide a potential route to extending the current two-month shelf life guideline from BI for NVP syrup when filled in an individual oral-dosing syringe (and sealed in the foil pouch).[8]
- Provide a potential route to combined packaging for both the maternal and infant doses of NVP.
- Increase the overall quality assurance for distribution of NVP syrup to HIV-positive pregnant women prior to labor/delivery by standardizing packaging practices using known and validated designs.
- Ultimately increase the coverage of NVP syrup provided during ANC visits.

Ultimate Goals and Objectives of HealthTech Project

The goal is to reduce mother-to-child-transmission of HIV by improving antiretroviral therapy coverage in PMTCT programs through developing, evaluating, and facilitating introduction of improved single-dose packaging solutions for NVP. In order to achieve this goal, PATH will:

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[5] Stringer E, Sinkala M, Stringer J, et al. Prevention of mother-to-child transmission of HIV in Africa: success and challenges in scaling up a nevirapine-based program in Lusaka, Zambia. *AIDS*. 2003;17:1377–1382.

[6] Viramune is a registered trademark of Boehringer Ingelheim.

[7] Exacta-Med is a registered trademark of Baxa Corporation.

[8] Boehringer Ingelheim. *Guidelines for the Administration of Viramune 200 mg Tablets and 50 mg/ml Oral Suspension for the use in Prevention of Mother to Child Transmission of HIV-1 (Where Single-Dose Prophylaxis with Viramune is Indicated)*. 2004.

- Develop, evaluate, and introduce an improved packaging solution (self-sealing foil pouch) which can be adopted in current PMTCT programs without requiring or relying on any change by BI to its current shelf-life guidelines for NVP suspension in an Exacta-Med dispenser.
- Pursue, possible extensions of BI's shelf-life guidelines for NVP syrup in an oral-dosing syringe when packaged in the improved foil pouch, through technical collaboration with BI on stability studies.

Status of Project as of September 2005

A number of potential single-dose packaging solutions for NVP syrup were evaluated during the initial years of this project. Developments in late 2004 resulted in a shift in project direction from a higher volume, more centralized packaging strategy to a PMTCT clinic-based approach of "filling and packaging on demand of the client." This approach requires the doctor or nurse to hand fill an Exacta-Med dispenser with a single dose of NVP syrup and seal it in a foil pouch specifically designed for this purpose. This solution addresses an immediate need in the field to improve the quality and ease of providing wrapping protection for NVP-filled dispensers without a need to change the current BI shelf-life guidelines of two months and also provides the potential for extending the BI shelf-life guideline if planned stability studies provide supporting data.[9]

In July 2005, PATH staff traveled to Kenya and met with program managers and PMTCT site staff. During meetings, the managers and staff all expressed that the self-sealing foil pouch would be a significant improvement in comparison to their current inconsistent practices of wrapping the NVP-filled syringes for ANC distribution. Program managers felt it would add additional program flexibility and value if BI would extend its shelf-life guidelines for self-sealing, foil-pouched NVP prefilled in dispensers beyond the current two-month guideline for NVP prefilled in dispensers (unpouched). The main benefit cited was the improved ability to provide an HIV-positive pregnant woman with both the maternal and infant doses of NVP during the first—and possibly only—ANC visit, which often occurs prior to the current two-month window for infant-dose NVP provision. At the same time, both managers and PMTCT site staff emphasized that the self-sealing foil pouch would represent a significant immediate improvement over current practices even without any extension in shelf life.

In August 2005, PATH staff met with key BI staff to provide an update on development of foil pouching options, discuss PATH's findings from the Kenya visit, and get BI's feedback and input on plans for moving forward. BI representatives expressed strong support for the self-sealing pouch approach. With the recent positive and significant feedback from PATH's Kenya visit and meeting with BI, the PATH team formulated an overall strategy and detailed Product Development Plan (PDP) for moving this important project forward with the

[9] Boehringer Ingelheim. *Guidelines for the Administration of Viramune 200 mg tablets and 50 mg/ml Oral Suspension for the Use in Prevention of Mother to Child Transmission of HIV-1 (Where Single-Dose Prophylaxis With Viramune is Indicated)*. 2004.

intention of getting an improved packaging option into the field as soon as possible. This PDP was approved by USAID in September 2005.

Milestones expected in the past six months	Achievements and progress towards milestones
Final results for study to determine effectiveness of foil pouch to decrease moisture loss of NVP in Exacta-Med dispenser.	Evaluation results reconfirmed the heat-sealed foil pouch is an effective means of decreasing moisture loss of NVP in Exacta-Med dispenser. The first adhesive test, however, did not prevent moisture loss (August 2005).
Plan and initiate stability studies of NVP in pouched Exacta-Med dispenser at BI. PATH role will likely be to supply the filled, pouched samples for the study.	PATH and its partners agreed that it was not prudent to initiate stability studies until a better performing adhesive seal pouch candidate has been identified. In the interim, BI has agreed to conduct high-performance liquid chromatography (HPLC) testing on samples from PATH's evaporative loss evaluation to measure potency and confirm that preventing moisture loss will lead to increased shelf life.
Support USAID's development of a revised structure and plan for the next phase of the project, taking into account the constraints of filling and pouching Exacta-Med dispensers with NVP for on-demand use.	Meetings in Kenya in August 2005 confirmed that local program managers and PMTCT staff felt the foil pouch would be considered a positive approach to providing NVP to expectant mothers. The main benefit cited was the improved ability to provide an HIV-positive pregnant woman with both the maternal and infant doses of NVP during the first—and possibly only—ANC visit, which often occurs prior to the current two-month window for infant-dose NVP provision. In September 2005, USAID approved PATH's revised plan to move forward. This plan moves on parallel tracks working to introduce improved packaging as soon as possible and to identify a packaging solution with potential for shelf-life extension.

Problems encountered	Actions taken or plans to resolve
During evaporative loss testing, the first adhesive tested on a foil pouch did not prevent moisture loss.	PATH is working with adhesive experts such as the 3M Company to identify an adhesive that will prevent moisture loss. PATH is also looking at mechanical ways to seal a foil pouch which would not require electricity (crimping for example).

Milestones expected in the next six months	Planned activities to reach those milestones
Plans and initiation of a pilot introduction of the self-sealing foil pouch at PMTCT/ANC sites in Kenya. This introduction is being conducted in collaboration with Elizabeth Glaser Pediatric AIDS Foundation and others.	PATH is writing the introduction protocol and will guide it through the human subjects protection committee review as well as an government review in Kenya. PATH will supply the foil pouches to support the pilot introduction and also develop training tools and job aids for use in the introduction.
Design and development of a prototype foil pouch which can enclose the NVP-filled oral syringe (infant dose) in one compartment and the NVP 200 mg tablet (maternal dose) in a separate but attached compartment.	Work with foil pouch vendors to review dual compartment pouching options. Select initial design, and produce initial prototypes.
Identification of an adhesive that serves as moisture barrier for NVP-filled Exacta-Med dispensers in a foil pouch.	PATH will meet with technical experts to identify lead candidate adhesives. PATH will conduct preliminary evaluations to screen the candidates and determine which should move forward into formal stability studies.
Plan and initiation of stability studies of NVP in pouched Exacta-Med dispenser at BI.	PATH's role will be to review the testing protocol and supply the filled, pouched samples for the study.

Semiquantitative Test for CD4+ Cell Count Determination

Health Need Addressed

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that nearly 40 million people are currently living with HIV infection who are eligible for treatment with antiretroviral (ARV) therapies. Ninety-five percent of these HIV-infected people are living in resource-limited settings.

Current treatment guidelines call for the use of CD4+ lymphocytes and HIV viral-load tests to determine when to start treatment in infected persons, to assess how well a treatment regimen is working, and to aid in determining when to switch to alternative drug regimens. For patients on established treatment, regular monitoring of CD4+ lymphocytes is recommended at three-month intervals. When new treatments are started, monitoring may be even more frequent.

Structured treatment interruptions or treatment protocols where patients are taken off all anti-HIV medications for periods of time in order to stimulate their immune systems also require careful and frequent monitoring using CD4+ lymphocytes and viral-load tests.

There are ever increasing numbers of HIV-positive individuals in developing countries, especially in Africa and Asia, who will continue to overburden and overwhelm health care services. Existing facilities to monitor CD4+ lymphocytes counts in HIV-positive individuals are either limited or absent in most developing countries because the available test methods are too expensive and complex. The decreasing cost and increasing availability of drugs makes palliative treatment of HIV-positive individuals more feasible in the developing countries where the disease is most prevalent.

HealthTech IV Solution and Potential Impact

Availability of a simple, inexpensive, semiquantitative method for monitoring CD4+ lymphocytes could have substantial public health impact, especially at a time when the availability of ARV therapy is becoming much more likely and widespread. To speed the development of an effective and commercially viable product, PATH searched the scientific literature and commercial market for available technologies that could be adapted or directly used for CD4+ cell count monitoring in the developing world. Two technologies, one for CD4+ cell purification from whole blood and one for estimation of CD4+ cell counts, were identified and evaluated: (1) Dynal CD4 positive isolation kit (Dynal Corporation, Oslo, Norway); and (2) the PortaScience PortaWBC™[1] flow-through cassette used for assessing mastitis status in dairy cows. We hypothesized that combining these technologies would allow clinicians or laboratory technicians in resource-limited settings to classify HIV-positive

[1] PortaWBC is a trademark of PortaScience.

patients into clinically important categories (sufficient: >500 cells/µl; borderline 200-500 cells/µl; and insufficient <200 cells/µl). Using funds from the Doris Duke Foundation, PATH worked on the first stages of the feasibility of this approach over the last year or so. Now, with funds from USAID to complement this work, we propose an accelerated timeline and schedule of activities to develop a suitable, affordable test in short order.

A sample of the semiquantitative colorimetric CD4+ T-cell detection system.

Ultimate Goals and Objectives of HealthTech Project

A simple, semiquantitative test for monitoring CD4+ cell counts in HIV-positive populations will:

- Allow health care workers to quickly and accurately monitor the immunological status of their HIV-positive patients.
- Provide data for clinicians making important decisions about initiating, stopping (through structured treatment interruption), or changing antiretroviral therapy drug regimens.
- Eliminate the most important barrier to appropriate distribution of drug therapies that reduce morbidity; reduce viral load, and therefore reduce transmission; and most importantly empower clinicians and patients to control the expanding epidemic.

Status of Project as of September 2005

Since the funding from USAID for this project just started in the summer of 2005, this report is focused on plans over the next six months instead of the past. More information is available in the product development plan.

Milestones expected in the next six months	Planned activities to reach those milestones
Reach a decision point about the need for a purification system in the assay.	• Evaluate PortaWBC membrane characteristics for adherence of red and white blood cells. • Evaluate membrane volume capacity. • Evaluate antibody adherence to membrane. • Evaluate alternative negative selection CD4+ purification systems.
Assess the feasibility of a fluorescent detection and reader system.	• Procure CD4+ antibody conjugates. • Identify handheld reader candidates. • Identify fluorphores and excitation and emission wavelengths. • Conduct preliminary experiments on new system with blood specimens if reader is available.

Strategic Objective 5

Rapid Diagnostics for Tuberculosis

Health Need Addressed

Tuberculosis (TB), the disease produced by the bacterium *Mycobacterium tuberculosis*, continues to cause significant morbidity and mortality worldwide. Recently, the increasing incidence of TB—particularly in the developing world—has been associated with HIV infection, the emergence of multiple drug-resistant strains, and the breakdown of preexisting screening programs. Globally, TB is already the leading cause of death among people with AIDS, accounting for about 40 percent of fatalities in Africa. While worldwide reporting reflects incomplete data, it is estimated that globally as many as 3 to 4 million deaths can be attributed to TB each year. Astonishingly, this figure exceeds the estimate for malaria or acute respiratory infections and ranks TB as one of the most important infectious disease problems today. The available data indicate that 95 percent of the clinical cases and 98 percent of the deaths attributable to TB occur in the developing world.

The general consensus is that the top priority for TB-control programs should be active case detection, confirmation of infection, and therapy for all infectious cases in both low- and high-prevalence areas. Since 1996, the World Health Organization (WHO) has promoted the Directly Observed Therapy Short Course (DOTS) strategy for TB control, one aspect of which is case detection through sputum smear microscopy of TB suspects. The emphasis on TB diagnosis by sputum smear microscopy is, however, problematic. The method is simple and relatively inexpensive but requires quality microscopes, experienced microscopists, and exacting quality control. The specificity of smear microscopy has been reported to be as high as 99.2 percent, but reports of sensitivity range from 40 to 60 percent for a combination of three examinations and may be as low as 20 to 25 percent in high HIV sero-prevalent populations (personal communication, Michael Iademarco, Centers for Disease Control and Prevention).

In developing countries, diagnostic sensitivity may be improved by sputum culture. However, a sputum culture takes weeks to yield results and requires dedicated equipment and technical expertise. Long delays can result in the patient being treated empirically and inappropriately, and the cost of some of the current culture systems may also be beyond what many control programs in resource-poor countries can afford. Recently, several new diagnostic methods for TB have been developed, including nucleic acid detection and amplification techniques. Although they provide advantages in terms of sensitivity, these methods are still too technically complex and expensive for use in most developing-country settings.

HealthTech IV Solution and Potential Impact

Serodiagnostic technology offers the potential for development of rapid, inexpensive tests for TB. They can be fairly simple to use, formatted as high- (e.g., ELISA-based assays) or low-volume assays (e.g., immunochromatographic strip tests [ICS]), and can be relatively inexpensive. There have been efforts to develop TB serodiagnostic tests for many years, but early tests had unacceptably low specificity. High test specificity is required because a false positive result can commit the patient to a long course of inappropriate therapy, with risk of stigma, high costs of antibiotics, and the potential for side effects.

For the developing world, inexpensive and less complex serodiagnostic tests can be developed in simple dipstick, strip, or particle agglutination formats, which can be performed in clinics with lower patient volumes. These could be used at the peripheral or district health care level to fortify syndromic diagnosis of TB in sputum-positive patients and to detect suspected cases of sputum-negative or extra-pulmonary TB. This would be especially effective in specialty applications (e.g., testing of HIV-positive persons), since the clinical signs and symptoms of TB are often atypical, and skin test anergy may be present.

The development of a TB ICS test could provide an alternative diagnostic tool to supplement or replace microscopic diagnosis of TB-positive sputum smears or identify suspected cases of TB-negative sputum smears or extra pulmonary TB infection and therefore will:

- Extend or enhance immediate or same-day return of results in intermediate to peripheral hospitals and clinics to allow appropriate therapy to be administered.
- Provide a back-up tool to microscopic examination of stained sputum smears for use in central or specialty clinics where high-volume diagnosis is currently performed well.
- Potentially reduce testing costs through technology transfer for commercial manufacturing in the developing world.

Ultimate Goals and Objectives of HealthTech Project

- To develop an accurate and simple serodiagnostic test for TB that is affordable to populations in the developing world.
- To understand the need and market for rapid diagnostics for TB in order to make informed decisions about investments in development of tests.

Status of Project as of September 2005

TB ICS test development has been discontinued due to poor results from field trials in Botswana, India, and Ukraine. PATH has started to evaluate the feasibility of a phage-based approach to a point-of-care test for tuberculosis. Meanwhile the study of the need and market for a rapid TB test is ongoing. Additionally, we are currently negotiating a collaborative arrangement with a private-sector company that is developing a TB diagnostic patch test. We are hopeful that this test will provide accurate diagnosis in resource-poor settings.

Milestones expected in the past six months	Achievements and progress towards milestones
Proof of principle attained for a phage-based TB assay.	We are still compiling preliminary data on the phage-based system.
Explore funding opportunities for new TB diagnostics.	Ongoing.
A final plan for the TB market analysis.	Plan has been written up and will be forwarded to USAID soon. Title now reads: "Assessing laboratory quality, activity and distribution: A comparison of existing assessment tools and guidance for investments in laboratory networks given the potential of new diagnostic technologies"

Problems encountered	Actions taken or plans to resolve
Early TB phage experiments provided negative results.	Experiments are being repeated with newly calibrated lab equipment.

Milestones expected in the next six months	Planned activities to reach those milestones
Collaboration with Sequella, another private-sector company with an existing TB test, to promote the use of their TB patch test in resource-poor settings.	Visit to Sequella in Rockville, MD, in November/December 2005. Signing of a two-way confidential disclosure agreement for both parties. Formal discussions about possible introduction studies or advocacy work with global health stakeholders.
Decision point reached about the feasibility of a phage-based TB assay.	Preliminary experiments on phage growth and replication.
Implementation of the market analysis and assessment of current TB diagnostic practices in laboratories in Africa.	The PATH DC office will carry out and report on the assessment to USAID as well as the Gates Global Forum on Diagnostics.

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